REMARKS

Claims 1, 3-5, 14, 21 and 23-24 are pending after entry of the amendments set forth herein. Claim 22 is canceled without prejudice. Claim 1 is amended. Support for these amendments is found throughout the specification, for example, at page 8, lines 2-3 and 13-15, page 23, lines 24-26, page 28, lines 3-5, and in Claim 22. Claims 23 and 24 are added. Support for these claims is found throughout the specification and the claims as originally filed, for example, at page 18, lines 10-14, at paragraph 57, and at page 26, lines 20-29. No new matter is added. As such, the Examiner is requested to enter the above amendments.

INTERVIEW SUMMARY:

Applicants thank Examiner Dutt, Examiner Stucker and Examiner Kolker for the courtesy of conducting an interview on April 14, 2010 with Applicant's representatives Pamela Sherwood and Elizabeth Alcamo to discuss the rejections in the Final Office Action. Applicant's representatives proposed claim amendments to overcome the rejections of record. The Examiners provided additional suggestions.

REJECTIONS UNDER §103(A)

I. Claims 1, 3, 14 and 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kondo et al. (Brain Res 791: 352-356, 1998), in view of Plevova (Radiol Oncol 36: 33-40, 2002), as evidenced by Kyrkanides et al. (Mol Brain Res. 104: 159-169, 2002).

II. Claims 1, 3-5, 14 and 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tada et al. (Neurosurgery 41: 209-219, 1997 – online publication 1-18 pages), in view of Plevova, (Radiol Oncol 36: 33-40, 2002).

III. Claims 1, 3-5, 14 and 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kondo et al. (Brain Res 791: 352-356, 1998), in view of Plevova, (Radiol Oncol 36: 33-40, 2002).

Newly amended Claim 1 recites the steps of: "identifying an individual at risk for suffering from loss of neurogenesis resulting from chronic neuroinflammation due to cranial irradiation"; "contacting said individual with a dose of a non-steroidal anti-inflammatory drug (NSAID) that crosses the blood-brain barrier, which dose is effective to reduce

neuroinflammatory activity by recruitment or activation of monocyte/microglial cells"; and "measuring cognitive function following cranial irradiation, wherein a progressive decline in cognitive function is linked to impaired neurogenesis; wherein said loss of neurogenesis resulting from chronic neuroinflammation due to said cranial irradiation in an individual is reduced."

This method arises from recognition on the part of the inventors of the present application that:

- a decline in cognitive function is observed following chronic neuroinflammation, e.g. from cranial irradiation or LPS;
- this decline in cognitive function is chronic and progressive in nature, i.e. impairment in cognitive function does not stabilize over time, but rather continues to decline over the long term;
- this progressive decline in cognitive function is due to an inability to make new neurons, i.e. "a loss of neurogenesis capacity" or "loss of neurogenesis"; and
- this loss of neurogenesis capacity, and hence progressive decline in cognitive function, can be reduced by the administration of an NSAID.

For the claims to be anticipated or obvious, the Office must show that the ordinarily skilled artisan has performed the steps of the invention or would possess the necessary insight to make obvious the steps of the invention, i.e. identifying an individual subjected to cranial irradiation, administering an NSAID that crosses the blood-brain barrier to the individual in a dose effective to reduce chronic neuroinflammatory activity; and measuring cognitive function following the cranial irradiation, to determine if a progressive decline in cognitive function is present.

Such insight would require knowledge that cranial irradiation induces chronic neuroinflammation, and that the irradiation-induced chronic neuroinflammation induces a loss of neurogenesis, measurable as a progressive decline in cognitive function. Furthermore, the ordinarily skilled artisan would also have to recognize that NSAIDs could interfere with the induction of loss of neurogenesis.

Applicants submit that one of ordinary skill in the art would not be able to predict from the cited combinations of art that a progressive decline in cognitive function due to cranial irradiation-induced chronic neuroinflammation could be reduced by administering an NSAID.

I. Kondo et al. in view of Plevova as evidenced by Kyrkanides et al.

Applicants submit that the cited combination of art does not make obvious the pending claims. The primary reference, Kondo et al., teaches that ischemia induces delayed hippocampal neuronal cell death, and that indomethacin treatment significantly protects against this death (abstract, Fig. 1, Fig. 2). However, as evidenced by Liu et al. (of the record) and as asserted in previous responses, ischemia is associated with an *increase* in neurogenesis, not a loss of neurogenesis. Thus, teachings such as those by Kondo on ischemia and conditions arising therefrom are irrelevant to a discussion of methods of reducing loss of neurogenesis.

The secondary reference fails to remedy the deficiencies of the primary reference. The secondary reference, Plevova et al., teaches ionizing radiation. Plevova et al. was cited by the Examiner for teaching that "ionizing radiation results in an inflammatory reaction and cellular damage" (Office Action, June 10, 2009, p. 10-12). However, Plevova et al. provides no teachings on ischemia to contradict the teachings of Liu and establish relevance of the primary reference to the methods of the pending claims. Indeed, Plevova et al. is silent on ischemia. Accordingly, it is unclear to the Applicant how Plevova et al. can be combined in *any* manner with the primary reference. Accordingly, Plevova fails to remedy the deficiencies of Kondo.

Kyrkanides et al. was cited as evidence that one of ordinary skill in the art would be motivated "to use indomethacin in models of cranial irradiation based on evidence showing that cyclooxygenase 2 or COX-2 mRNA is induced in the mouse brain following irradiation in a dose dependent manner, as well as in ischemic cerebral injury." (Office Action, June 10, 2009 p. 7, l. 3-7). However, relevant to the pending rejection, Kyrkanides provides no teachings to contradict the teachings of Liu and establish relevance of the primary reference to the methods of the pending claims. Likewise, Kyrkanides provides no teaching of a relationship between ischemia (as taught by Kondo) and irradiation (as taught by Pelvova) that would suggest to the ordinarily skilled artisan that they should combine the primary and the secondary references.

> In response to previously presented arguments, the Examiner asserts that:
>
> both ischemia and cranial irradiation are known to cause neuroinflammation. For example, Price et al. (J.Med Primatol 30:81-87, 2001) teaches that neuroinflammation is observed after irradiation of the brain in primates resulting in the activation of microglia/macrophages (abstract)." (Final Office Action, p. 4, l. 10-13) (emphasis added)

Applicants note that, as indicated by this sentence by the Examiner, this teaching by Price is with regards to irradiation, not ischemia. Furthermore, a careful review of Price et al. yields no teaching on ischemia. Accordingly, Price et al. is *irrelevant* to the teachings of Kondo.

> In response to previously presented arguments, the Examiner also asserts that:
>
> Applicant's arguments with regards to ischemia and stimulation of neurogenesis are persuasive in part. It is noted that only certain regions of the brain demonstrate ischemia induced neurogenesis. For example, Liu et al (J Neurosc 18: 7768-7778, 1998 -submitted by Applicant) show that only the dentate gyrus elicits neurogenesis, whereas other regions of the CNS like hippocampal CA1 neurons, the entorhinal cortex and lateral striatum exhibit neuronal loss following global ischemia (Abstract; page 7771, col 2, para 4-5; Figures 5E, 6C). Similar findings were reiterated in the Yamashima reference (also submitted by Applicant) (abstract). The fact that some regions of the brain demonstrate neurogenesis after ischemia, Applicant's generalized allegation that ischemia results in neurogenesis is incorrect. Please note that the claims do not recite the effect on neurogenesis in any particular nuclei of the brain.

First, as indicated by the Examiner, Liu et al. does teach that ischemia promotes neurogenesis. Thus, Applicant's generalized statement that ischemia promotes neurogenesis is, in fact, correct. Furthermore, it is well known in the art that neurogenesis occurs in some regions of the brain, e.g. the dentate gyrus, the subventricular zone, and does not occur in others, e.g. regions in which mature neurons reside such as the CA1 zone of the hippocampus, and cortex (this includes the entorhinal cortex) and the striatum (this includes the lateral striatum). Thus, one of ordinary skill in the art *would not expect* to see neurogenesis in the regions that did not demonstrate neurogenesis as observed by Liu and as recited by the Examiner. Indeed, if neurogenesis were observed in these locations, the ordinarily skilled artisan would be very surprised. Moreover, in view of this understanding in the art of where neurogenesis does and does not occur in the brain, one of ordinary skill in the art would know exactly where to look to observe neurogenesis, and thus, reciting these locations in the claims would not be required. Finally, as noted above, the claims as amended include the step of measuring cognitive function, where a progressive decline in cognitive function serves as a surrogate biomarker for impaired neurogenesis; accordingly, no step of measuring loss of neurogenesis *per se* is necessary.

Thus, Applicants maintain that, as evidenced by Liu et al. (of the record), ischemia is associated with an *increase* in neurogenesis, not a loss of neurogenesis, and thus that the

reference by Kondo is irrelevant to a discussion of methods of reducing loss of neurogenesis such as those recited in the pending claims.

In view of the aforementioned deficiencies, it is clear that the cited combination of art does not provide the ordinarily skilled artisan with the knowledge that cranial irradiation induces chronic neuroinflammation, that the irradiation-induced chronic neuroinflammation induces a loss of neurogenesis, measurable as a progressive decline in cognitive function, and that NSAIDs could interfere with the induction of loss of neurogenesis. Thus, the ordinarily skilled artisan would not be able to predict from the cited combination of art that a progressive decline in cognitive function due to cranial irradiation-induced chronic neuroinflammation could be reduced by administering an NSAID.

Applicants submit that new claims 23 and 24 are also patentable for at least these reasons.

Withdrawal of the rejection is respectfully requested.

II. Tada et al. in view of Plevova.

Applicants submit that the cited combination of art does not make obvious the pending claims. The primary reference, Tada et al., teaches that cranial irradiation produces edema and subsequent vascular and inflammatory changes, and necrosis, and that dexamethasone may protect against the cranial irradiation-induced edema but not necrosis (Abstract, last paragraph). However, relevant to the presently claimed method which recites "contacting an individual with a dose of a non-steroidal anti-inflammatory drug (NSAID)", dexamethasone is not an NSAID; dexamethoasone is a glucacortacoid, which is a steroidal anti-inflammatory; see, e.g. Plevova, page 34, col. 1 (cited in this rejection). Thus, Tada et al. does not teach contacting an individual with an NSAID.

The secondary reference does not remedy the deficiencies of the primary reference. As discussed above, Plevova et al. (the secondary reference) was cited by the Examiner for teaching that "ionizing radiation results in an inflammatory reaction and cellular damage" (Office Action, June 10, 2009, p. 6, l. 10-12, and page 8, paragraph 23). However, Plevova et al. does not teach the use of NSAIDs to protect against ionizing radiation-induced neuroinflammation. The only teaching in Plevova et al. related to radiation-induced effects on the brain is on the wide use of dexamethasone as a prophylaxis of radiation induced brain oedema and inflammation (p. 34, col. 1, l. 22-24). No discussion of radiation-induced effects on the brain or the reduction of such effects is provided in Plevova's discussion of the use of NSAIDs (see p.

34, paragraph bridging col. 1 and 2). Accordingly, Plevova et al. does not remedy the deficiencies of Tada.

In view of the aforementioned deficiencies, it is clear that the cited combination of art does not provide the ordinarily skilled artisan with the knowledge that cranial irradiation induces chronic neuroinflammation, that the irradiation-induced chronic neuroinflammation induces a loss of neurogenesis, measurable as a progressive decline in cognitive function, and that NSAIDs could interfere with the induction of loss of neurogenesis. Thus, the ordinarily skilled artisan would not be able to predict from the cited combination of art that a progressive decline in cognitive function due to cranial irradiation-induced chronic neuroinflammation could be reduced by administering an NSAID.

Applicants submit that new claims 23 and 24 are also patentable for at least these reasons.

Withdrawal of the rejection is respectfully requested.

III. Kondo et al. in view of Plevova.

Applicants submit that, as discussed above, the cited combination of art does not make obvious the pending claims. The primary reference by Kondo et al. teaches ischemia, which, as evidenced by Liu et al., is irrelevant to a discussion of methods of reducing loss of neurogenesis and hence the methods of the pending claims. The secondary reference, Plevova et al., fails to remedy the deficiencies of the first reference, since it provides no teachings on ischemia to contradict the teachings of Liu and establish relevance of the primary reference to the methods of the pending claims. In view of these deficiencies, the ordinarily skilled artisan would not be able to predict from the cited combination of art that a progressive decline in cognitive function due to cranial irradiation-induced chronic neuroinflammation could be reduced by administering an NSAID.

Applicants submit that new claims 23 and 24 are also patentable for at least these reasons.

Withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-303.

Respectfully submitted,
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